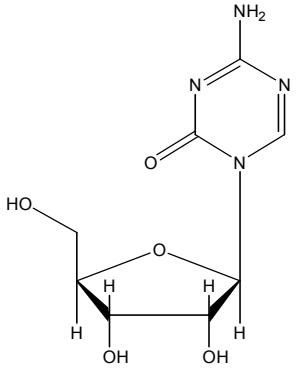
AZACITIDINE
CAS No. 320-67-2
First Listed in the *Eighth Report on Carcinogens*



CARCINOGENICITY

Azacitidine (5-Azacytidine; 5-AzaC) is *reasonably anticipated to be a human carcinogen* based on evidence of malignant tumor formation at multiple tissue sites in multiple species of experimental animals (NCI 42, 1978; Luz and Murray, 1988; IARC V.50, 1990).

5-AzaC, when administered by intraperitoneal (i.p.) injection, induced lymphoreticular neoplasms and skin and lung tumors in male and/or female mice (NCI 42, 1978; Luz and Murray, 1988; multiple studies reviewed in IARC V.50, 1990), and leukemia, lymphoma, and tumors of the liver and lung in offspring of treated pregnant dams (IARC V.50, 1990). In male rats, 5-AzaC administered i.p. induced squamous cell carcinoma of the skin and interstitial-cell tumors of the testes, and appeared to increase the incidence of non-testis tumors in male offspring of treated dams (IARC V.50, 1990).

There are no data available to evaluate the carcinogenicity of azacitidine in humans.

ADDITIONAL INFORMATION RELEVANT TO CARCINOGENESIS OR POSSIBLE MECHANISMS OF CARCINOGENESIS

Using an initiation-promotion experimental design, a chronic i.p. treatment of male rats acutely administered *N*-nitrosodiethylamine (DEN) after partial hepatectomy with 5-AzaC synergistically increased the frequency of liver tumors and of lung and skin tumors (Carr et al., 1988; IARC V.50, 1990).

The carcinogenic/enhancement activity of 5-AzaC has been postulated to result directly or indirectly from its ability to inhibit DNA methylation (Harrison et al., 1983; for reviews, see Kerbel et al., 1984; Kerbel et al., 1986; Takenaga, 1986; Glover et al., 1987; Glover and Leyland-Jones, 1987; Jones and Buckley, 1990; Haaf, 1995). Altered levels of DNA methylation can affect gene expression (for reviews see Cedar, 1988; IARC V.50, 1990; Fajkus et al., 1992; Velge et al., 1995), with hypomethylation being associated with the expression of genes that are normally silent or downregulated (Jones et al., 1983; Nyce et al., 1983; Riggs and Jones, 1983; Collard et al., 1989; Jones and Buckley, 1990; Pascale et al., 1993). In addition, 5-AzaC in the absence of metabolic activation is positive in a wide variety of prokaryotic, lower eukaryotic, and

mammalian *in vitro* test systems, inducing DNA damage, mutations (base-pair substitution mutations only) in prokaryote systems; mitotic recombination, gene conversion, and gene mutations in somatic and germ cells of lower eukaryotes (yeast, *Drosophila*, plants), and DNA damage, chromosomal aberrations, mutations (but not point), and morphological transformation in cultured mammalian cells. Studies to evaluate the genetic activity of 5-AzaC in somatic cells of mammals have not been reported; however, it was reported as negative for dominant lethal mutations in mice.

There are no data available to suggest that the mechanisms thought to account for tumor induction by 5-AzaC in experimental animals would not operate also in humans.

PROPERTIES

5-AzaC is a white crystalline powder which has a melting point of 235-237 ^{o}C. It is soluble in warm water, cold water, 0.1 N hydrochloric acid, 0.1 N sodium hydroxide, 35% ethanol, acetone, chloroform, hexane, and dimethyl sulfoxide. 5-AzaC is very unstable in aqueous media, with rapid degradation to complex products occurring within hours of dissolution in intravenous solutions at room temperature. It is most stable at pH 7, when its half-life is about 5 days. When heated to decomposition, 5-AzaC emits toxic fumes of nitrogen oxides (NO_x). The commercial product is available as a lyophilized powder in vials containing 100 mg of the compound with 100 mg mannitol for reconstitution as injections of 5 mg/mL.

USE

5-AzaC is a cytostatic agent that has been mainly used as an investigational drug since the l970s for the treatment of acute leukemia. It is administered via intravenous (i.v.) and intramuscular (i.m.) injection and i.v. infusion, at a daily level of 40 to 750 mg/m^2. It is used alone or in combination with vincristine, vinblastine, prednisone, cytarabine, or amsacrine, at a daily dose of 50-150 mg 5-AzaC/m^2. 5-AzaC has also been tested for use in the treatment of a variety of solid tumors (IARC V.50, 1990). 5-AzaC has been used clinically in cancer treatment trial protocols in combinations with other antineoplastic agents such as doxorubicin, amsacrine and etoposide, and Granulocyte Colony Stimulating Factor (NCI/PDQ, 1996).

PRODUCTION

5-AzaC is synthesized in Germany. It can be prepared by synthetic methods or can be isolated from a culture of the bacterium *Streptoverticillium ladakanus* (IARC V.50, 1990). No data on imports or exports of 5-AzaC were available. The 1993 Chem Sources USA directory identified 13 U.S. suppliers and 2 foreign suppliers of 5-AzaC (Chem Sources USA, 1993). Chem Sources (1996) listed 14 U.S. suppliers of 5-AzaC, including the NCI Chemical Carcinogens Reference Standard Repository. The 1998 *Chemical Buyers Directory*, however, only names one current domestic supplier of the chemical (Tilton, 1997).

EXPOSURE

The primary routes of potential human exposure to 5-AzaC are intravenous and intramuscular injection and intravenous infusion. It is administered at a daily level of 40-750 mg/m^2. 5-AzaC is used alone or in combination with vincristine, vinblastine, prednisone,

cytarabine, or amsacrine, at a daily dose of 50-150 mg/m^2 5-AzaC (IARC V.50, 1990). Potential occupational exposure may occur for workers formulating or packaging the solutions and for health care professionals administering the drug. The National Occupational Exposure Survey (1981-1983) indicated that 1,069 workers, including 699 women, potentially were exposed to 5-AzaC (NIOSH, 1990). This estimate was derived from total observations of the use of the actual compound (48%) and tradename products (52%).

REGULATIONS

According to a monograph in the 1996 *Handbook on Injectable Drugs (HID)* entitled "Azacitidine Investigational" (Drug Information Fulltext, 1996), azacitidine is still an investigational drug. Its investigational number is NSC-102816. No regulatory information was found in the 1996 *Code of Federal Regulations* titles 21, 29, or 40.